Efficacy and Safety of Emapalumab in Adults with Macrophage Activation Syndrome (MAS) Secondary to Still's Disease: Results from a Pooled Analysis of Two Prospective Trials

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CONCLUSIONS

- Emapalumab is well tolerated and efficacious in adults with MAS in Still's disease who had an inadequate response to glucocorticoids (GCs), offering meaningful improvements in clinical signs and symptoms of MAS and laboratory parameters
- Limitations include small sample size and a need for more studies of MAS in adult-onset Still's disease (AOSD)

INTRODUCTION

- MAS is a life-threatening complication of Still's disease, characterized by interferon gamma (IFNγ)-driven macrophage activation and systemic hyperinflammation[1–3]
- The estimated prevalence of MAS in AOSD is 9%, with a poor prognosis and high mortality[4–6]
- Emapalumab, an anti-IFNγ antibody, binds free and receptor-bound IFNγ, providing rapid and targeted neutralization of IFNγ[7]
- Emapalumab is FDA-approved for primary HLH and secondary HLH/MAS in known or suspected Still's disease[8]
- Emapalumab has demonstrated safety and efficacy in patients with MAS in Still's disease with an inadequate response to high-dose GCs in two clinical trials (NCT03311854 [NI-0501-06] and NCT05001737 [NI-0501-14])[8–10]
  - These studies had predominantly pediatric cohorts (age <17 years)
- Further characterization of emapalumab treatment outcomes in adults with MAS secondary to Still's disease may enhance the understanding of targeted IFNγ neutralization and help inform treatment decisions in this high-risk population

OBJECTIVE

- To evaluate outcomes in adults with MAS associated with Still's disease treated with emapalumab

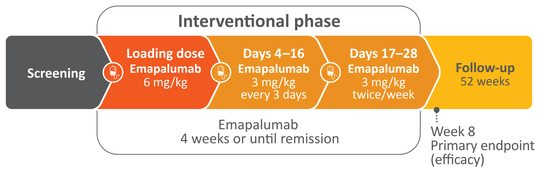
METHODS

- Data were pooled for adults (age ≥17 years) from two prospective, open-label, single-arm interventional studies with similar study designs in patients with MAS in Still's disease who had an inadequate response to high-dose GCs (NCT03311854 [NI-0501-06] and NCT05001737 [NI-0501-14]; **Figure 1**)

Inclusion criteria

- A diagnosis of active MAS where the patient was febrile, had a serum ferritin level >684 ng/mL, and any two of:
  - Platelet count ≤181 × 109/L;
  - Aspartate aminotransferase (AST) levels >48 U/L;
  - Triglycerides >156 mg/dL;
  - Fibrinogen levels ≤360 mg/dL

Figure 1: Study design[a]



[a]Emapalumab dose could be increased, or dosing interval could be shortened, at the investigator's discretion.

Inclusion criteria (continued)

- An inadequate response to high-dose intravenous (IV) GC treatment administered for ≥3 days as per local standard of care, including, but not limited to, pulses of 30 mg/kg methylprednisolone on 3 consecutive days
  - In cases of rapid worsening of the patient's condition and/or laboratory parameters, inclusion could occur <3 days after starting high-dose IV GCs
- The current analysis included only patients aged ≥17 years at the time of treatment

Exclusion criteria

- A diagnosis of primary hemophagocytic lymphohistiocytosis (HLH) or HLH consequent to a neoplastic disease
- Patients treated with canakinumab, Janus kinase inhibitors, tumor necrosis factor α inhibitors, tocilizumab, etoposide (for MAS), or anakinra >4 mg/kg/day at the time of emapalumab initiation

Endpoints

- The primary endpoint of the pooled analysis was a complete response at Week 8 according to an 8-component composite endpoint comprising the MAS clinical activity score (VAS ≤1/10 cm; absence of MAS clinical signs and symptoms) plus:
  - White blood cell and platelet counts above the lower limit of normal;
  - Lactate dehydrogenase, AST and alanine aminotransferase <1.5 × the upper limit of normal;
  - Fibrinogen >100 mg/dL; and
  - Ferritin decreased by at least 80% from baseline and <2000 ng/mL
- Partial response was defined as VAS <4 cm and normalization of ≥3 of the abnormal baseline laboratory parameters
- GC tapering was defined as a reduction in dose to the same (or lower) dose being administered before the occurrence of MAS (in those patients who had already been treated for AOSD), or by ≥50% of the dose administered at emapalumab treatment start (in those patients who presented with MAS at Still's disease onset)

BASELINE CHARACTERISTICS

- 9/39 patients in the pooled cohorts were adults and included in this analysis (6 [66.7%] females; median age, 20 years [range, 17–64 years]) (**Table 1**)
- One patient had a prior episode of MAS

Table 1: Demographics and baseline characteristics of adult patients with MAS in Still's disease (N=9)

	N=9
Age, years, median (range)	20 (17–64)
Sex, female, n (%)	6 (66.7)
Geographic region, n (%)	
North America	1 (11.1)
Europe/UK	7 (77.7)
Japan	1 (11.1)
Weight, kg, median (range)	60.0 (45.0–77.4)
MAS clinical activity score (VAS), cm, median (range)	7 (4–9)

MAS, macrophage activation syndrome; VAS, visual analog scale.

RESULTS

Response rates

- At Week 8, 3/9 (33.3%; 95% CI, 7.5–70.1%) patients had a complete response
  - 5/8 (62.5%; 95% CI, 24.5–91.5%) patients assessed at Week 8 had an overall (complete + partial) response (**Figure 2**)

Figure 2: Response rates in adults with MAS in Still's disease receiving emapalumab who were assessed at Week 8 (n=8)[a]

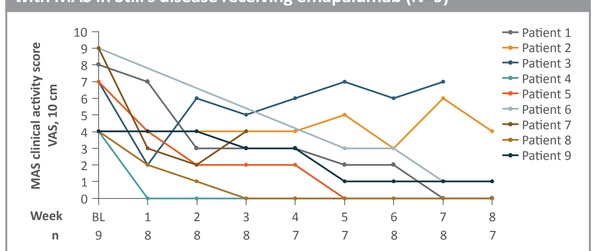


[a]One patient who died at Day 24 was not assessable. [b]No complete response nor partial response (n=1), no complete response, partial response not applicable (n=1). A patient is classified as no complete response, partial response not applicable if no complete response for the visit and <3 laboratory parameters used to determine complete/partial response were evaluable at baseline. [c]A patient is classified as not evaluable if all parameter values used to determine complete response are missing even after applying the imputation rules as described in the statistical analysis plan.
MAS, macrophage activation syndrome.

MAS clinical activity score

- Median MAS clinical activity score decreased from 7/10 cm (range, 4–9; n=9) at baseline to 0 (range, 0–4; n=7) at Week 8 (**Figure 3**)

Figure 3: Changes in MAS clinical activity score VAS (10 cm) in adults with MAS in Still's disease receiving emapalumab (N=9)

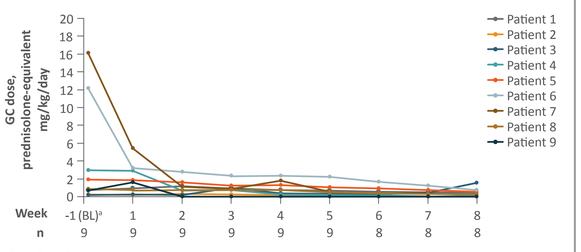


BL, baseline; MAS, macrophage activation syndrome; VAS, visual analog score.

Glucocorticoid tapering

- GC tapering was reported in 7/8 (87.5%; 95% CI, 47.3–99.7%) assessed patients at Week 8
- Median (range) GC dosing was 1.0 (0.2–16.1) prednisolone-equivalent mg/kg/day at baseline compared with 0.4 (0–1.6) mg/kg/day at Week 8 (**Figure 4**)

Figure 4: Changes GC dosing in adults with MAS in Still's disease receiving emapalumab (N=9)



[a]Study Days -7 to -1 (week prior to first dose of emapalumab).
BL, baseline; GC, glucocorticoid; MAS, macrophage activation syndrome.

Pharmacodynamic markers

- Chemokine C-X-C motif ligand 9 (CXCL9; a biomarker primarily induced by IFNγ activity), ferritin levels (a marker of disease activity), and soluble CD25 (sCD25; a marker of T-cell activation) decreased from baseline through Week 8 (**Table 2**)

Table 2: Change in pharmacodynamic markers in adults with acute MAS treated with emapalumab

Median (range)	Baseline	Week 8
CXCL9, ng/L	1914 (848–438,010) n=7	144 (below LLQ–190) n=3
Ferritin, mg/L	7240 (451–345,950) n=9	98 (7–811) n=7
sCD25, ng/L	9247 (2947–27,522) n=9	2765 (583–8530) n=6

CXCL9, chemokine C-X-C motif ligand 9; LLQ, lower limit of quantitation; MAS, macrophage activation syndrome; sCD25, soluble CD25.

Safety

- Forty-one treatment-emergent adverse events (TEAEs) were reported in 7 (77.8%) patients; 21 TEAEs in 5 (55.6%) patients were considered related to emapalumab (**Table 3**)
- Ten serious AEs (SAEs) were reported in 4 (44.4%) patients; 4 SAEs in 2 (22.2%) patients were considered related to emapalumab
- Eight infection TEAEs were observed in 6 (66.7%) patients; most were mild or moderate in intensity
- Seven infusion-related reactions were reported in 3 (33.3%) patients; none were serious
- One (11.1%) patient discontinued emapalumab because of a TEAE (pneumonia [Day 56])
- Two (22.2%) patients died (multi-organ dysfunction syndrome [Day 56] and shock [Day 24]; n=1 each), both considered unrelated to emapalumab

Table 3: TEAEs in adults with acute MAS treated with emapalumab (N=9)

	n (%)	Events
Any TEAE	7 (77.8)	41
Treatment-related	5 (55.6)	21
Serious TEAE	4 (44.4)	10
Treatment-related	2 (22.2)	4[a]
TEAE leading to treatment discontinuation	1 (11.1)	1
IRR	3 (33.3)	7
Serious	0	0
Infection TEAE	6 (66.7)	8
CMV infection	1 (11.1)	1
CMV infection reactivation	3 (33.3)	3
Pneumonia	2 (22.2)	2
Sepsis	1 (11.1)	1
Device-related sepsis	1 (11.1)	1

[a]Pneumonia (n=1), sepsis (n=1), MODS (n=1), pulmonary arterial hypertension (n=1).
CMV, cytomegalovirus; IRR, infusion-related reaction; MAS, macrophage activation syndrome; MODS, multiple organ dysfunction syndrome; TEAE, treatment-emergent adverse event.

Disclosures
B. Fautrel: Personal Income / Compensation with: AbbVie, Amgen, Biogen, BMS, Celltrion, Chugai, Eli Lilly & Co, Fresenius Kabi, Janssen, Medac, MSD, Nordic Pharma, Novartis, Pfizer, Sandoz, Sanofi, Sobi, UCB; **N. Blank:** Research Grant / Support with: Novartis, Sobi; Personal Income / Compensation with: Novartis, Sobi; Organizational Benefit with: Novartis, Sobi; **M. Gattorno:** Research Grant / Support with: Fresenius Kabi, Novartis, Sobi; Personal Income / Compensation with: Boehringer Ingelheim, Fresenius Kabi, Kiniksa, Novartis, Sobi; **D. Schwartz:** Research Grant / Support with: Eli Lilly & Co, Sobi; Personal Income / Compensation with: Electra, Sobi; **S. Vastert:** Research Grant / Support with: Sobi; Personal Income / Compensation with: Novartis, Sobi; **Y. Zhao:** Employee with: Sobi, Inc.; **H. Bodenstab:** Employee with: Sobi, Inc.; **E. Burillo:** Employee with: Sobi; **B. Jamieson:** Employee with: Sobi, Inc.; **F. de Benedetti:** Research Grant / Support with: Alphasigma, Novartis, Regeneron, Sanofi, Sobi; Personal Income / Compensation with: Novartis.

Acknowledgements
This study was funded by Sobi. The authors wish to acknowledge the investigators, participants and their families for their contribution to the studies. The authors also wish to acknowledge Kathleen York, CMPP from Sobi (Basel, Switzerland) for publication coordination and Caitlin Berry-Kilgour, PhD of Kainic Medical Communications Ltd. (Dunedin, New Zealand) for medical writing and editorial support, funded by Sobi, based on the authors' input and direction, and in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022).

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